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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/749,709	LIU ET AL.	
	Examiner	Art Unit	
	Robert M. Kelly	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4 and 6-13* is/are pending in the application.

4a) Of the above claim(s) *9-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,12 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 July 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *2/14/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendments of 4/6/05 and arguments of 7/14/04 are entered.

Claims 3 and 5 are cancelled. (It is noted that Applicant provided the text of the claim in the listing of the claims, but also indicated in the arguments that such claim was cancelled. Therefore, the claims are cancelled. However, for future reference, Applicant should not present the text of a claim that is cancelled, pursuant to 37 CFR 1.121(c).)

Claims 1-2, 4, and 6-8 are amended.

Claim 13 is newly presented.

Claims 1-2, 4, and 6-13 are presently pending.

Examiner Reassignment

This Application has been reassigned to Examiner Robert M. Kelly, of Art Unit 1632, Technology Center 1600. All future correspondence should address Examiner Kelly as the Examminer.

Election/Restrictions

Pursuant to the restriction requirement of 12/13/02, and Applicant's subsequent election of 3/10/03, of Group I, claims 1-8 and 12, drawn to a method of producing transgenic animals, wherein the method comprises pronuclear injection, and indicated in the Official Action of 2/10/04, p. 2, Claims 9-11 are withdrawn from prosecution, and claims 1-8 and 12-13 are examined to the extent that the methods comprise pronuclear injection.

However, after review of the restriction requirement of 12/13/02 and election of 3/10/03 by the Examiner, it is felt that the restriction requirement was improper, and claim 1 should be treated as a linking claim for each of inventions I-III. Therefore, upon a finding of an otherwise-allowable linking claim (i.e., Claim 1), the claims that embrace inventions II-III will be considered to the extent that they contain the same scope of any otherwise-allowable linking claim. In addition, to make the record clear, the claims will be considered with respect to any animal, including humans, because the Examiner finds that also addressing humans, instead of non-human animals, would not pose an undue burden in this instance.

Therefore, Claims 1-8 and 12-13 are considered for the scope of methods drawn to pronuclear injection.

Information Disclosure Statement

Applicant's information disclosure statement of 2/14/04 provides French document, No. FR 2 782 734. Applicant has not provided an English translation of such document, and hence the document has not been considered. Such is indicated by the lack of initials next to such citation and the crossing-out of the citation.

Specification

The specification is objected to, because, on page 4, paragraph 1, the last sentence of the specification references "the accompanying FIGURE", while Applicant supplies two figures in the amendment of 7/14/04. Applicant is required to correct the deficiency by specific reference to a figure, or other language to indicate what figures to reference.

Drawings

The drawings are objected to because the drawings do not match the brief description of the drawings. Specifically, the brief description references a single figure, while Applicant has now amended the drawings to contain two figures: figure 1A and figure 1B. Moreover, while the brief description of the drawings references a method, the drawings appear to be representations of plasmids used in the methods. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner,

the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Objections

The objection to claim 5 is withdrawn in view of Applicant's cancellation of such claim.

The objections to claim 1 for containing periods and for containing the term "result" are withdrawn in light of Applicant's amendments and arguments.

Claims 1, 2, and 8 remain objected-to for containing non-elected subject matter, however, such objection is held abeyance in light of the changes to the restriction/election (above), as well as Applicant's arguments of 7/14/04.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

In light of Applicant's cancellation of claims 3 and 5, the rejections of such claims under 35 USC 112, second paragraph, as being indefinite for failing to point out and distinctly claim the subject matter which applicant regards as the invention, are rendered moot, and thus are withdrawn.

In light of Applicant's amendments and arguments the rejection of claim 1 for containing the phrased "such as", "the toxin gene", "the toxin transgene", and "the toxic gene" are withdrawn.

In light of Applicant's amendment and argument, the rejections of claims 4 and 6-8 under 35 USC 112, second paragraph, are withdrawn.

Claims 1-2, 4, 6-8, and 12-13 remain or are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, for reasons of record and/or reasons necessitated by the amendments.

Claim 1 remains rejected under 35 USC 112, second paragraph, for being incomplete as written and indefinite as written. To further explain these rejections, the following explanation is provided by the Examiner:

Claim 1 encompasses a method of "altering the offspring sex ratio of an animal", while the method steps appear to be directed to creating a transgenic animal with the phenotypic characteristic of having an altered offspring sex ratio in comparison to the parents of such animal. As such, the claim does not alter the offspring sex ratio of that animal. The object of the method is further unclear because the claim step d) identifies animals with "desireable reproduction feature, specifically, alteration of offspring's sex ratio". While it appears this statement alone indicates that the alteration of the offspring's sex ratio is required, in light of the method not matching the preamble, it is further not clear what other characteristics may suffice, nor how such alteration of sex ratio would occur, and hence, the term "specifically, alteration of offspring's sex ratio" may not be a requirement, but an optimal characteristic.

Claim 1 is also rejected for containing any linkage between the step of identifying and the other steps of the claim. Specifically, the step of identifying requires identifying at least one transgenic animal with desireable reproduction feature. It is unclear whether what is meant is the

identification of a transgenic animal created in step b), a female animal transgenic for Cre recombinase activity of step c), or whether the step simply requires screening all transgenic animals for the characteristic of producing offspring with an altered sex ratio.

Further, Claim 1 now also recites the terms "a Herpes Simplex Virus promoter (HSV) promoter". It is not clear how a promoter can be promoted by another promoter. Genes have only one promoter, and it is not expressed.

Claim 1 also now recites the limitation "the post-meiotic spermatogenesis-specific promoter". There is insufficient antecedent basis for this limitation in the claim.

Claim 1 also now recites the limitation "an optional loxP site-flanked intervening DNA sequence inserted between the ... promoter and the toxin". The DNA does not contain a toxin, but encodes the toxin.

Claim 1 also now recites, for step c) "mating the males of the said transgenic animals with females, the females containing Cre recombinase activity to activate the said transgene wherein the transgene includes the optional loxP site-flanked intervening DNA sequence ...". It is not clear whether the males not containing the optional loxP site-flanked intervening DNA sequence are also required to be mated with the females containing such activity, or whether they may be mated to any female.

Claims 2, 4, 6-8, and 12-13 are rejected for depending from claim 1 and not overcoming the lack of clarity in such base claim.

Claim 4 now recites the term "the alteration of offspring's sex ratio of said transgenic animals is from 50% to 100%". This term lacks clarity because it is unclear how the alteration of sex ratio is determined in terms of percentages. Specifically, the claim would normally be read

as a change of 50% to 100% (i.e., if the offspring was normally 50/50, male/female, the alteration could be 25/50 or 50/25, which would be a change leading to a ratio of 50%) but the ratio for 100% (i.e., change to 100/0 or 0/100) would be an undefined ratio or a ratio of 0 in such analysis, which is never 100%. Obviously, from the Examiner's analysis, this percent alteration is confusing and lacks clarity. Correction, or persuasive explanation of how the Examiner is misinterpreting the statement, along with a persuasive explanation of how these terms are properly interpreted, is required.

Claim 8 is rejected because it is unclear how claim 8 relates to the parent claim, claim 1. To wit, for example, does the replacement of the post-meiotic spermatogenesis-specific regulatory sequence occur after creating the transgenic animal of claim 1, step b? Or, alternatively, is the initial construct modified, in which case this claim is an improper dependent claim, because it fails to further limit the base claim, but instead would encompass a completely different method.

Claim 8 recites the term "further comprising the steps of" ... inserting a modified version of the DNA sequence from Claim 1 into sex chromosomes, preparing another DNA sequence, creating transgenic animals, and breeding such animals with other transgenic animals comprising a Cre recombinase-encoding sequence under the control of spermatogenesis or oogenesis-specific promoters. As such, it is unclear how the steps in claim 1 are to be accomplished, because the DNA sequence of Claim 1 is modified and can no longer be used in the steps contributed from claim 1. Further it is unclear how these new steps relate to the method of altering the offspring sex ratio of an animal in claim 1. The Examiner recommends writing an

independent claim to encompass this material, if Applicant is simply trying to write a claim that encompasses ZW organisms.

Claim 8 recites the term "inserting a transgene bearing said DNA sequences". It is unclear whether this transgene is the modified construct described before the method steps, or whether it is a new construct without any operable linkage.

Claim 8 recites the term "inserting a transgene ... onto one of the two sex chromosomes prevents embryos with one particular sex chromosome from developing into individuals." It is unclear how the inserted transgene could prevent any particular embryo with any particular sex chromosome from developing into individuals.

Claim 8 recites the limitation "the promoter". There is insufficient antecedent basis for this limitation in the claim.

Claim 8 recites the limitation "the toxin gene". There is insufficient antecedent basis for this limitation in the claim. Moreover, the promoter would be considered part of the artificial gene to which Applicant appears to be referring, therefore, a sequence could not be placed between such promoter and the gene it is within.

Claim 8 recites the limitation "said transgene". There is insufficient antecedent basis for this limitation in the claim. Specifically, is Applicant referring to the transgene which is the modified transgene of claim 1, or the gene construct described wholly in claim 8?

Claim 8 does not appear to relate to the method of claim 1, from which it depends. Specifically, claim 1 is a method for altering of the offspring sex ratio of an animal. It is unclear how one alters the sex ratio of the animals at any stage, and, due to the lack of clarity, it is also unclear how these limitations relates at all to claim 1 (see above rejections).

Claim 13 recites the limitation "wherein the selectable marker of step a) ii) is selected from the group ...."; however, Claim 1 does not have a selectable marker in step a) ii), but instead has one in step a) iii). For purposes of compact prosecution, this limitation will be read as limiting the selectable marker of step a) iii).

Claim 8 not further considered

Due to the lack of clarity in claim 8, as delineated above, the Examiner cannot perform any meaningful examination of the claim, and as such, the claim is not considered beyond this point.

Note to Applicant – claim interpretation

Due to the extreme lack of clarity in the claims, and the fact that the Examiner is required to perform a compact prosecution, the Examiner is interpreting claim 1 to encompass two different methods, which are so different the Examiner finds it difficult to encompass both methods in a single claim, and therefore, the claim is interpreted in the following two forms:

Claim 1A: A method for producing a transgenic animal that, when bred to a wild-type animal of that species, produce offspring ratios that differ from the ratio generally observed when two wild-type animals of that species are bred, the method comprising:

(a) preparing a transgene, which transgene includes, in operable association:

(i) one or more copies of one or more promoters chosen from the group consisting of: the HSV promoter, the HSV promoter in mutated form, and the HSV promoter in truncated form;

(ii) a sequence encoding a toxin chosen from the group consisting of: thymidine kinase, thymidine kinase in mutant form, and thymidine kinase in truncated form;

(iii) an optional sequence encoding a marker;

(iv) an optional cellular localization signal sequence that prevents mRNAs and proteins produced from the artificial transgene from diffusing among interconnected spermatids; and

(v) two optional flanking DNA sequences allowing said transgene to be inserted onto specific loci of a sex chromosome by homologous recombination;

(b) creating transgenic animals using said transgene so that the transgene is inserted onto one of the two sex chromosomes (which the Examiner interprets to mean that if the two optional flanking DNA sequences allowing said transgene to be inserted onto specific loci of a sex chromosome by homologous recombination are present, such is used for the creation);

(c) mating the male transgenic animals created with transgenic females, which females express a transgene for Cre recombinase; and

(d) determining, from the produced offspring, those males that produced offspring ratios that are altered from that of wild-type matings of the same species; and

Claim 1B: A method for producing a transgenic animal that, when bred to a wild-type animal of that species, produce offspring ratios that differ from the ratio generally observed when two wild-type animals of that species are bred, the method comprising:

(a) preparing a transgene, which transgene includes, in operable association:

(i) one or more copies of one or more promoters chosen from the group consisting of: the HSV promoter, the HSV promoter in mutated form, and the HSV promoter in truncated form;

(ii) a sequence encoding a toxin chosen from the group consisting of: thymidine kinase, thymidine kinase in mutant form, and thymidine kinase in truncated form;

(iii) an optional sequence encoding a marker;

(iv) a loxP site-flanked intervening DNA sequence inserted between the one or more copies of one or more promoters and the sequence encoding the toxin;

(v) an optional cellular localization signal sequence that prevents mRNAs and proteins produced from the artificial transgene from diffusing among interconnected spermatids; and

(vi) two optional flanking DNA sequences allowing said transgene to be inserted onto specific loci of a sex chromosome by homologous recombination;

(b) creating transgenic animals using said transgene so that the transgene is inserted onto one of the two sex chromosomes (i.e., the first generation) (which the Examiner interprets to mean that if the two optional flanking DNA sequences allowing said transgene to be

inserted onto specific loci of a sex chromosome by homologous recombination are present, such is used for the creation);

(c) mating the male transgenic animals (i.e., the first generation male) created with transgenic females of that species containing an expressed transgene for Cre recombinase (i.e., this is a new female transgenic animal, unrelated the previously-made animals);

(d) Obtaining male offspring (i.e., second generation male) from step (c);

(e) mating the second generation males of step (d) with wild type females of that species; and

(f) determining, from the progeny yielded from each mating, those males that produced offspring ratios that are altered from that of wild-type matings of the same species.

Claim Rejections - 35 USC § 112 – written description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

In light of Applicant's amendments and arguments the rejections of claims 6-7 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is withdrawn.

In light of the Examiner's inability to address claim 8, the rejection of such claim under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for

reasons of record in the Official Action of 2/10/04, pp. 9-11, is maintained until such time as the claim becomes clear enough for the examiner to determine whether the rejection should be maintained.

Claim 1-7 and 12 remain rejected, and claim 13 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for reasons of record in the Official Action of 2/10/04, pp. 9-11, for the genera of any HSV-tk in mutant or truncated form. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Because the scope of the rejection has changed, due to the amendments, and for clarity, the rejection will be re-addressed, along with the following rejection, in the same body of rejection.

Claims 1-7 and 12-13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-7 and 12-13 encompass:

(i) any HSV promoter, in wild-type, mutated, or truncated form, that is a post-meiotic spermatogenesis-specific regulatory sequence;

(ii) any mutated or truncated form of HSV-tk that interferes with a sperm's ability to fertilize an oocyte;

(iii) any cellular localization sequence that restricts the ability of the mRNA and protein expressed from the transgene to randomly diffuse among the inter-connected haploid spermatids;

(iv) any flanking sequences that allow the transgene to be inserted onto any specific loci of any sex chromosome by homologous recombination; and

(v) the alteration of any animal's offspring sex ratio.

With regard to the various genera, the specification broadly states, respectively:

(i) the HSV-1 tk gene may be used, with a cryptic promoter of such gene, which is spermatogenesis-specific (p. 4, paragraph 2), and upon review of one of the cited references (Al-Shawi, et al. (1991) Molec. Cell. Biol., 11(8): 4207-16), it is clear that a single promoter is within the coding region of the HSV-1 tk gene, and permits expression of a gene before meiosis (ABSTRACT); therefore not even Applicant's single disclosed promoter is a post-meiotic spermatogenesis-specific promoter;

(ii) any HSV-1 thymidine kinase may be used (p. 4, paragraph 2);

(iii) no cellular localization sequences have been described at all;

(iv) any sequence from the Hprt locus (p. 8, paragraph 3), any sequence from the Tspy locus (Id.), and any loci on any sex chromosome that is accessible by transcription machinery in spermatids and where an insertion does not cause an abnormal phenotype (p. 6, paragraph 2);

(v) methods of making animals that produce offspring with altered sex ratios compared with wild-type animal matings (pp. 2-3).

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by

describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan could determine the desired effect. Hence, the analysis below demonstrates that Applicant has not determined the core structure for full scope of the claimed genera.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. In the instant case, as described above, respectively:

(i) the HSV-1 tk gene may be used, with a cryptic promoter of such gene, which is spermatogenesis-specific (p. 4, paragraph 2), and upon review of one of the cited references (Al-Shawi, et al. (1991) Molec. Cell. Biol., 11(8): 4207-16), it is clear that a single promoter is within the coding region of the HSV-1 tk gene, and permits expression of a gene before meiosis (ABSTRACT); therefore not even Applicant's single disclosed promoter is a post-meiotic spermatogenesis-specific promoter;

(ii) any HSV-1 thymidine kinase may be used (p. 4, paragraph 2);

(iii) no cellular localization sequences have been described at all;

(iv) any sequence from the Hprt locus (p. 8, paragraph 3), any sequence from the Tspy locus (Id.), and any loci on any sex chromosome that is accessible by transcription machinery in spermatids and where an insertion does not cause an abnormal phenotype (p. 6, paragraph 2);

(v) methods of making animals that produce offspring with altered sex ratios compared with wild-type animal matings (pp. 2-3). However, the specification does not provide any disclosure as to what would have been the required structure which would:

(i) be any HSV promoter that is post-meiotic spermatogenesis-specific;

(ii) be any thymidine kinase;

(iii) restrict the ability of the mRNA and protein from randomly diffusing among interconnected haploid spermatids;

(iv) cause homologous recombination in any sex chromosome where it is accessible to transcription machinery and does not cause an abnormal phenotype; or

(v) any method of altering any animal's offspring sex ratio. Next then, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (i.e., other than nucleotide sequence), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case, the only other characteristics are the functional characteristics discussed above.

Such functional characteristics, however, do not allow one of skill in the art to distinguish the different members of the genera from each other.

Applicant's attention is directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

In conclusion, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of any HSV promoter that is a post-meiotic spermatogenesis-specific regulatory element, any thymidine kinase, its mutated, or truncated forms, any cellular localization sequence that restricts an mRNA or protein from diffusing among the interconnected spermatids, any flanking sequences that allow homologous recombination into any sex chromosome at any point that is accessible to transcription machinery and does not cause any abnormal phenotype, or the alteration of any animal's offspring sex ratio at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Response to Argument – written description

Applicant's arguments of 7/14/04 are considered, but are deemed to not fit the present rejection, and hence are not addressed.

Claim Rejections - 35 USC § 112 – enablement

In light of the cancellation of claims 3 and 5, the rejections of such claims under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, are rendered moot, and thus, are withdrawn.

In light of the difficulties in interpreting claim 8, the rejection of such claim under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, are held in abeyance (see above for explanation).

Claims 1-2, 4, 6-7 and 12 remain rejected, and claim 13 is newly rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

For clarity, and in light of the Examiner's interpretation of claim 1 (ABOVE), the rejection is restated, and added to, below; however, as a first step, Applicant's methods are not methods for altering the offspring ratio of an animal, but for creating an animal with a phenotype of producing altered offspring ratios when bred with a wild-type animal of that species, because the specification only describes this method, and does not describe how to modulate the offspring ratio produced from any specific animal. Secondly, the methods require that the animal be male, because step c of claim 1 requires the animal to be bred to a female, and females cannot be bred to females, as well as the fact that the promoter is a post-meiotic spermatogenesis-specific promoter, and therefore cannot work in females which do not have any cells that undergo spermatogenesis. Therefore, the claims are interpreted within this context, but

Applicant is advised that such should also be considered when amending the claims, because it is part of the enablement.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Such a determination is not a simple factual consideration, but is a conclusion reached by weighing at least eight factors as set forth in In re Wands, 858 F.2d at 737, 8 USPQ.2d at 1404. Such factors are:

(1) The breadth of the claims;

(2) The nature of the invention;

(3) The state of the art;

(4) The level of one of ordinary skill in the art;

(5) The level of predictability in the art;

(6) The amount of direction and guidance provided by Applicant;

(7) The existence of working examples; and

(8) The quantity of experimentation needed to make and/or use the invention.

These factors will be analyzed, in turn, to demonstrate that one of ordinary skill in the art would have had to perform "undue experimentation" to make and/or use the invention within its full-claimed scope, and that, therefore, Applicant's claims are not enabled.

The Breadth of the Claims

Claim 1, from which all the claims depend, is interpreted to encompass two different methods, which are each considered broad. In addition, dependent claims 2, 4, 6-7 and 12 are

broad, because they do not sufficiently focus the scope of the broad limitations of claim 1 to any enabled scope.

Claim 1 encompasses two embodiments, the scope of which is provided above (section labeled "Note to Applicant". Claim 2 limits the animals to any organism using X and Y chromosomes to determine sex. Claim 4 limits the ratio of the offspring's sex ratio to between 50 and 100%. Claim 6 limits the optional sequences for insertion in specific loci of the sex chromosome to Hprt locus-specific sequences. Claim 7 limits the optional sequences for insertion in specific loci of the sex chromosome to Tspy pseudogene-specific sequences. Claim 12 limits the techniques of creating transgenic animals to several methods, including the elected pronuclear injection method, and examining the integration site by FISH for each transgenic founder to search for individuals with the transgene inserted onto the desired sex chromosome. Claim 13 limits the selectable marker to one of four genes.

Because these claims encompass altering the offspring sex ratio of any animal, creating any sex of any transgenic animal with altered offspring sex ratios, any HSV promoter, any thymidine kinase, any loxP site flanked intervening sequence, any specific loci of any sex chromosome, any method of creating transgenic animal, mating of a transgenic animal with any female containing Cre recombinase activity, any cellular localization sequence, alteration of sex ratios of 100%, and any alteration of sex ratios, the detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide area of knowledge, to a reasonably comprehensive extent. In other words, each of those aspects considered broad must be fleshed out to a reasonable extent so that one of ordinary skill in the art at the time of invention by Applicant (hereinafter the "Artisan"), would be able to practice the invention, and do so to the

fully-claimed scope of invention, without an undue burden being imposed on such Artisan (undue burden). However, as will be discussed below, this burden has not been met.

The Nature of the Invention and State of the Art

The invention is the nature of creating transgenic animals with a phenotype of producing offspring with altered offspring ratios, i.e., the ratio of male to female, compared to wild-type animal matings of the same species. However, the nature of transgenic animals is such that producing any specific phenotype is not reasonably predictable, which would cause the Artisan to have to perform undue experimentation to find the working embodiments.

The art of transgenic animals has for many years stated that unpredictability lies with the site or sites of integration of the transgene into the target genome. Transgenic animals are regarded to have, within their cells, cellular mechanisms which prevent expression of the transgene, such as DNA methylation or deletion from the geneome (Kappel, et al. (1992) Current Opinion in Biotechnology, 3: 549, col. 2, paragraph 2). Mullins et al. (1993) states that not all animals express a transgene sufficiently to provide a model for a disease as the integration of a transgene into different species of animal has been reported to give divergent phenotypes (Mullins, et al. (1993) Hypertension 22, page 631, col. 1, paragraph 1, lines 14-17). The elements of the particular construct used to make the transgenic animal are held to be critical, and that they must be designed case by case without general rules to obtain good expression of a transgene, e.g., specific promoters, presence or absence of introns, etc. (Houdebine (1994) J. Biotech., 34, page 281). "The position effect" and unidentified control elements also are recognized to cause abberant expression (Wall (1996) Theriogenology 45, page 61, paragraph 2, line 9 to page 62, line 3). Mullins et al. (1996) discloses that "the use of nonmurine species for

transgenesis will continue to reflect the suitability of a particular species for the specific questions being addressed, bearing in mind that a given construct may react very differently from one species to another." (Mullins, et al. (1996) J. Clin. Invest., 98, page S39, Summary). Well regulated transgenic expression is not frequently achieved because of poor levels or the complete absence of expression or leaky expression in non-target tissues (Cameron (1997) Molec. Biol., 7, page 256, paragraph bridging cols. 1-2). Factors influencing low expression, or the lack thereof, are not affected by copy number and such effects are seen in lines of transgenic mice made with the same construct (Cameron (1997) Molec. Biol., 7, page 256, lines 10-13). Further, Sigmund states that the random nature of transgene insertion, resulting founder mice can contain the transgene at a different chromosomal site, and that the position of the transgene effects expression, and thus, the phenotype observed (Sigmund (2000) Arteroscler. Throm. Vasc. Biol. 20, page 1426, col. 1, paragraph 1, lines 1-7). With regard to the import of promoter selection, Niemann states that transgenic pigs made with different promoters regulating expression of a growth hormone gene give disparate phenotypes – one deleterious to, the other compatible with, pig health (Niemann (1997) Transg. Res. 7, page 73, col. 2, paragraph 2, line 12 to page 74, col. 1, line 4).

Such differences in gene expression are also found in different transgenic mice expressing HSV-tk mutants (Al-Shawi, et al. (1988) Mol. Cell. Biol., 8(11): 4821-28, ABSTRACT), which does not correlate to the normal expression of the Mup gene, to which the HSV-tk is linked (ABSTRACT). Hence, even within a single species, the expression of genes for HSV-tk may be altered according to the specific transgenic animal made.

Hence, in light of the above analysis of the nature of the invention, the Artisan would require enough information to reasonably predict that any particular gene, driven by any particular promoter, and placed within any particular portion of the genome, would actually transcribe enough functional mRNA, and translate and process enough functional protein therefrom for a long enough period of time to effect the desired killing of specific sex-chromosome bearing sperm, in any particular species.

With regard to the use of transgenic animals expressing Cre recombinantly, such issues are compounded, as these Cre sequences are not only required to be expressed, but also to be expressed at a time after fertilization and before the formation of the germ-line cells. Hence, such expression is not reasonably predicted to occur and cause the removal of the optional loxP flanked sequence before such germ-line cells have already formed, and therefore, the Artisan would predict such cells to comprise the loxP flanked sequence, which would then not allow the production of any gene to kill the sperm carrying that particular sex chromosome. Lastly, it is noted that the use of a Cre recombinant female would appear to have no effect on the males without the loxP flanked site, and as such, the Examiner wonders why such mating is required. If there is information that affects the patentability of such matings to wild-type females, the Examiner requests such information, to better examine the case.

With regard to the use of selection markers, such selection markers are taught by the specification to allow for selection of properly-transformed cells when making transgenic animals; however in light of the effects of position within the genome, and species differences discussed above, it is not reasonably predictable that any particular integration will allow for such selection, due to differences in expression due to such position effects and species

differences. Hence, it is not reasonably predictable that these selection markers would even serve their purpose to begin with.

With regard to the use of any animal, it is clear that the invention, even if worked would not work for any animal, because those animals where the females carry the sex chromosomes, i.e., ZW organisms, would produce male animals with either no sperm, or all sperm, and such would still not alter the ratio of male to female, because the females' chromosome determines sex.

With regard to the use of any truncated or mutated form of HSV-tk, it is not reasonably predictable that any particular mutant of HSV-tk will provide the activity required to destroy the sperm before fertilization.

To wit, it has long been known how to mutate proteins, but it has been similarly long been known that such mutations are not reasonably predictive of activity for any particular protein. For example, Rudinger (1976) Peptide Hormones, University Park Press, Baltimore, MD., pp. 1-7 discusses the peptide hormones and the characteristics of amino acids as components of the peptide hormones (TITLE). (It is noted that Rudinger discusses peptide hormones, but the general areas of unpredictability are common to all proteins.) In doing so, Rudinger notes that many amino acids may be grouped according to general characteristic (pp. 1-3), and many of these are also classified in two or more classifications (p. 3). Hence, simple mutations of "type" are not reasonably predictable, because there are multiple types to any particular amino acid. Moreover, Rudinger finds that the context of any amino acid is important for structure (pp. 3-4), and that therefore, simple deletions, insertions, or substitutions are also not reasonably predictable, because not only is "type" important, but context is also important,

having longer-range effects than that of simply type. Further, Rudinger discusses the mechanisms of information transfer (e.g, binding and effecting a receptor, which is analogous to any protein binding anything and causing any particular effect) (pp. 4-5). In doing so, Rudinger finds that there exist "patterns" on molecules for recognition, which may involve amino acids close by in the amino-acid polypeptide sequence, or far away (Id.). As such the conformation of the whole molecule is important, and any particular amino acid change, deletion, or addition, may alter the conformation of the molecule enough to affect any particular binding and effect on another molecule.

> In analyzing the significance of such observations, Rudinger states that:
> In a given molecule, some amino acids or sequences obviously owe their 'significance' to their inclusion in the pattern which is directly involved in recognition by, and binding to, the receptor. However, the fact that the existence of this pattern is dependent on a conformation stabilized by intramolecular interactions, ..., implies that other amino acids or sequences contributing to this conformational stability will be no less 'significant' for the biological activity of the molecule.

(p. 5).

And, in conclusion, Rudinger states:

> The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study. The careful design of synthetic analogues, and their evaluation in biological systems which permit separate analysis of the various phases of hormone action, is the best way to obtaining such information.

(p. 6).

Bowie, et al. (1990) Science, 247 : 1306-10 provides similar insight into the lack of reasonable predictability for the mutation of any particular protein. To wit, Bowie discuses that while many substitutions may be tolerated, in other cases substitutions may not be tolerated at all (e.g., 1306, col. 2, paragraph 2). Moreover, the significance of surface and buried amino acids while is not reasonably predictable either (pp. 1306-07), surface sites may not have any

importance, but sometimes they are absolutely important due to binding (p. 1308), and predicting structure with reasonable predictability is generally limited to homologous proteins, but even that is difficult due to alignment problems (p. 1308). In general, Bowie continues to reflect the observations of Rudinger: it is not reasonably predictable that any particular amino acid change, deletion, or addition would provide a functional molecule with similar activity, and only painstaking analysis would provide such information for any particular change (e.g., pp. 1309-10).

Hence, the nature of the invention is not reasonably predictable for any of the particular proteins and genes claimed, due to the unpredictability of structure-function relationships.

Moreover, with regard to the HSV-tk, and its intended use in killing spermatids, Salomon, et al. (1995) Molec. Cell. Biol., 15(10): 5322-28, through exhaustive deletional analyses, identified specific HSV-tk mutants that act on gancyclovir as they would normally, but do not induce destruction of spermatids (ABSTRACT). Hence, any particular mutation may cause alterations that remove the lethality to spermatids, but not affect the generally-assayed behaviors of such molecules. Hence, in light of the structure-function relationships being not understood, and in light of the fact that HSV-tk mutants also exhibit this problem, it is not reasonably predictable that any particular mutant or truncation of HSV-tk would produce a protein that kills spermatids.

With regard to the use of cellular localization sequences for the mRNA and proteins, as well as proteins that act in a "no-random diffusion fashion among the interconnected spermatids", the Examiner knows of no art demonstrating that any sequence restricts the localization of such mRNA and/or protein, or that any protein may be so-localized among the

inter-connected spermatids. Without any such evidence of any specific protein or mRNA sequence or structure that would cause such localization, and given that the spermatids are connected by large openings, the Artisan would not reasonably predict that any such sequences exist, much less the structure required to make and use such sequences.

With regard to the use of any HSV promoter, HSV-tk promoter, in wild-type, mutant, or truncated form, on top of the problems with transgene expression, it is clear from Al-Shawi, et al. (1991) Molec. Cell. Biol., 11(8): 4207-16, that transgene expression in the spermatids only occurs from a single promoter of the HSV-1 tk gene, a cryptic TATA-box independent promoter located in the coding region of the testes (ABSTRACT). Hence, not any HSV promoter, or mutant or wild-type or truncated promoter will accomplish the intended expression, but only that promoter disclosed by Al-Shawi (Applicant is also reminded that this is not a post-meitoic spermatogenesis specific promoter either, as it works in pre-meiotic germ cells too, Id.).

The claims also embrace embodiments directed to homologous recombination (e.g., claim 1, step a)(vi)), and such may occur through the elected species of pronuclear injection as the means of producing the transgenic animal (e.g., dependent claim 12). Pronuclear injection relies on random integration of a transgene into the genome. It is not reasonably predictable in the art that random integration of a transgene would enable targeting to specific loci of the sex chromosomes.

Hence, to sum up, from the nature of the invention and state of the art, the artisan would require more information to reasonably predict that any particular gene, driven by any particular promoter, and placed within any particular portion of the genome, would actually transcribe enough functional mRNA, and translate and process enough functional protein therefrom for a

long enough period of time to effect the desired killing of specific sex-chromosome bearing sperm, in any particular species. Moreover, to exacerbate the issue, when mating such animals with females containing Cre recombinase activity, the Cre recombinase activity is also subject to position effects and species-specific differences in expression, which may preclude any action of Cre recombinase on the germ cells before sperm are made, and hence, more information is required by the artisan to reasonably predict that such matings would produce active transgenes in any particular animal species, given any particular position and expression pattern for the transgenes. Further, such use of selection markers is compounded by the same effects, and would not be reasonably predicted to even work for any particular species due to position effects and species specific differences in such expression. The artisan would also require further information to reasonably predict how to effect such methods in ZW organisms, because the females determine the sex, and the males produce the sperm. For the various mutants and truncations of HSV-tk, the artisan would require more information to reasonably predict which mutants and truncations produce the required activity on sperm. For the use of various HSV promoters, the Artisan would require more information to determine which promoters would produce such post-meiotic spermatogenesis-specific expression, as even the single promoter that does function during spermatogenesis is not a post-meotic promoter, but acts pre-meiotically. Lastly, the Artisan would require more information to reasonably predict that pronuclear injection could be used to produce homolgous recombination.

The Level of One of Ordinary Skill in the Art at the Time of Invention

The level of one of ordinary skill in the art at the time of invention was advanced, being that of a person holding a Ph.D. or an M.D.; however, because of the immaturity of the art, and

its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

The Level of Predictability in the Art

Because of the art, as shown above, does not disclose anything in any way similar to the methods claimed by Applicant, the Artisan could not predict, in the absence of further information to the contrary, that such applications would efficacious in making any transgenic animal with any particular phenotype, including the phenotype claimed (modulation of an animals offspring ratio), and the phenotype intended to be claimed (creation of an animal that produces offspring ratios that are altered compared to wild-type matings of the same species).

Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Direction and Guidance Provided by Applicant

Applicant's specification broadly discusses sex and the utility of creating animals that produce altered offspring ratios, compared with wild-type matings of the same species (pp. 1-2), a summary broadly covering claim language (pp. 2-3), the expression of toxins and subsequent destruction of cells (pp. 3-4), problems with cytoplasmic bridges between the interconnected spermatids (p. 4), HSV-tk and its involvement in the development of male mice that are sterile (p. 4), a variety of protocols to transform and make transgenic animals (p. 5), specific targets for integration (p. 5), the use of intervening loxP flanked sequences to create founder animals (p. 6),

and modified methods for targeting embryogenesis, presumably for use in female animals, and in ZW organisms (p. 7).

Further it should be noted that Applicant's argument in the specification that the HSV-tk expressed in mice do not interact with adjacent spermatids, is limited to the finding that male mice do not transmit the HSV-tk gene to the next generation, although many of these males are fertile (p. 4, paragraph 2). However, such does not exclude the possibility that there is diffusion, and such diffusion that is somewhat limited, and in such a case as half the spermatids being of the sex to be rendered infertile, it is not reasonably predictable that all of the spermatids would be rendered infertile.

Moreover, such does not constitute the specific direction and guidance the Artisan would require to reasonably predict that any particular gene, driven by any particular promoter, and placed within any particular portion of the genome, would actually transcribe enough functional mRNA, and translate and process enough functional protein therefrom for a long enough period of time to effect the desired killing of specific sex-chromosome bearing sperm, in any particular species. Moreover, to exacerbate the issue, when mating such animals with females containing Cre recombinase activity, the Cre recombinase activity is also subject to position effects and species-specific differences in expression, which may preclude any action of Cre recombinase on the germ cells before sperm are made, and hence, more information is required by the artisan to reasonably predict that such matings would produce active transgenes in any particular animal species, given any particular position and expression pattern for the transgenes. Further, such use of selection markers is compounded by the same effects, and would not be reasonably predicted to even work for any particular species due to position effects and species specific

differences in such expression. The artisan would also require more specific direction and guidance to reasonably predict how to effect such methods in ZW organisms, because the females determine the sex, and the males produce the sperm. For the various mutants and truncations of HSV-tk, the artisan would require more information to reasonably predict which mutants and truncations produce the required activity on sperm. For the use of various HSV promoters, the Artisan would require more information to determine which promoters would produce such post-meiotic spermatogenesis-specific expression, as even the single promoter that does function during spermatogenesis is not a post-meotic promoter, but acts pre-meiotically. Lastly, the Artisan would require more information to reasonably predict that pronuclear injection could be used to produce homolgous recombination.

The Existence of Working Examples

Applicant provides a prophetic working example protocol, but does not provide any evidence that the protocol would be reasonably predicted to work, even in mice, given the lack of reasonable predictability in the art and disclosure provided by Applicant.

Undue Experimentation

In light of the lack of reasonable predictability in the various aspects discussed, it would have required undue experimentation for the Artisan to reasonably predict whether any particular gene, driven by any particular promoter, and placed within any particular portion of the genome, would actually transcribe enough functional mRNA, and translate and process enough functional protein therefrom for a long enough period of time to effect the desired killing of specific sex-chromosome bearing sperm, in any particular species. Further undue experimentation would be required, to exacerbate the issue, when mating such animals with females containing Cre

recombinase activity, the Cre recombinase activity is also subject to position effects and species-specific differences in expression, which may preclude any action of Cre recombinase on the germ cells before sperm are made, and hence, further experimentation is required by the artisan to reasonably predict that such matings would produce active transgenes in any particular animal species, given any particular position and expression pattern for the transgenes. Further, such use of selection markers is compounded by the same effects, and would require further experimentation to be reasonably predicted to even work for any particular species due to position effects and species specific differences in such expression. The artisan would also require further experimentation to reasonably predict how to effect such methods in ZW organisms, because the females determine the sex, and the males produce the sperm. For the various mutants and truncations of HSV-tk, the artisan would require more experimentation to reasonably predict which mutants and truncations produce the required activity on sperm. For the use of various HSV promoters, the Artisan would require more experimentation to determine which promoters would produce such post-meiotic spermatogenesis-specific expression, as even the single promoter that does function during spermatogenesis is not a post-meotic promoter, but acts pre-meiotically. Also, the Artisan would require more experimentation to reasonably predict that pronuclear injection could be used to produce homolgous recombination. Lastly, the Artisan would be required to perform undue experimentation to find the versions of HSV-tk which would be limited to the spermatid which in which it is expressed.

Given the very large amount of experimentation, and the fact that not even a single embodiment would be reasonably predicted to work, it would have required undue

experimentation to find any working embodiment embraced by the claims, much less most of the working embodiments.

Conclusion

Due to the extreme amount of experimentation and lack of any reasonably predictable embodiment, the claims are not enabled whatsoever.

Response to Argument – Enablement

Applicant's arguments of 7/14/04 have been fully considered, but are not found persuasive.

Applicant argues that the constructs used would produce, with a high degree of certainty, animals with altered offspring ratio phenotypes, and that working examples are not required to be provided (pp. 9-10).

Such is not found persuasive. Applicant's argument fails to address a single area found to lack reasonable predictability and show how, through evidence or logic, such arguments presented by the Examiner are overcome. Mere assertion does not carry any weight. Moreover, with regard to the absence of example, while such example would certainly go a long way to finding something enabled, Applicant is not required to provide an example, but the specification should be reasonably predicted to work for the fully claimed scope, and, in light of the Examiner's arguments to a lack of reasonable predictability, the specification, in light of the art, does not overcome such arguments. Therefore, Applicant must either demonstrate by example, or argument and other evidence, why these areas of unpredictability do not apply to the instantly claimed invention, or are overcome by the instantly claimed invention.

Applicant argues that they have overcome the rejection based on promoters, tk genes, etc., by the newly limited version of promoters of HSV, their mutated or truncated forms, and HSV-tk, or in mutated or truncated form (p. 10, last paragraph).

Such is not persuasive. As is demonstrated above, none of these promoters are post-meotic spermatogenesis specific promoters, the mutations and truncations would not be reasonably predicted to form working and properly specific proteins, and only a single promoter is known to effect such expression during spermatogenesis.

Applicant argues that pronuclear injection is random, but a certain number of constructs would be predicted to have the proper integration in a particular chromosome of interest, which may be assayed for, and that the generation and subsequent characterization of multiple lines of transgenic animals is not "undue experimentation" because it is within the capability of the Artisan (Applicant's argument of 7/14/04, pp. 10-11, paragraph bridging).

Such is not persuasive. Undue experimentation is found because it is extensive, and because no single working embodiment would be predicted to work given the lack of reasonable predictability in the art and Applicant's disclosure, much less the majority of the working embodiments embraced by Applicant's claimed invention.

Applicant similarly argues that any species could be made, and the experimentation would be characterized as undue (Applicant's argument of 7/14/04, pp. 11-12, paragraph bridging).

Such is not persuasive for the same reasons as the previous argument. Undue experimentation is found because it is extensive, and because no single working embodiment would be predicted to work given the lack of reasonable predictability in the art and Applicant's

disclosure, much less the majority of the working embodiments embraced by Applicant's claimed invention. Applicant should provide scientific reasoning or evidence to overcome the areas of a lack of reasonable predictability to overcome the Examiner's argument, not conclusory statements of not undue experimentation and conclusory statements that the transgenes are predicted to work.

Similar argument is presented for the use of pronuclear injection and the use of homolgous recombination (p. 12).

Such is not persuasive for the same reasons as the previous argument. Undue experimentation is found because it is extensive, and because no single working embodiment would be predicted to work given the lack of reasonable predictability in the art and Applicant's disclosure, much less the majority of the working embodiments embraced by Applicant's claimed invention. Applicant should provide scientific reasoning or evidence to overcome the areas of a lack of reasonable predictability to overcome the Examiner's argument, not conclusory statements of not undue experimentation and conclusory statements that the transgenes are predicted to work.

Applicant argues that the prior rejection based on the use of Cre-expressing animals to mate with animals lacking of the optional loxP sites appear to have no relevance, is overcome by the present amendments (Applicant's argument of 7/14/04, pp. 12-13, paragraph bridging).

Such is not persuasive. As has been addressed above, Applicants claims require mating with Cre-expressing transgenic females, whether or not such animal has the loxP site flanked sequence. It is noted that Applicant is attempting to comply, but the Examiner suggests that such

problems would be better overcome if the separate embodiments were written in independent form, as provided in the interpretations provided by the Examiner above.

Applicant argues that the cells would not be destroyed by the toxin as presently claimed, and it is only expressed in sperm cells during spermatogenesis.

Such is persuasive, and the rejection on that basis is withdrawn. However, due to the position effects and species differences, discussed in the rejection above, it is still not reasonably predictable to produce the animals of the desired phenotype for the reasons provided above.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

In light of Applicant's cancellation of claims 3 and 5, the rejections of such claims under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,596,089 to Silversides, are rendered moot, and thus are withdrawn.

In light of Applicant's amendments and arguments, the rejections of Claims 1-2, 4, and 8 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,596,089 to Silversides, is withdrawn.

Claim Rejections - 35 USC § 102

In light of the cancellation of claims 3 and 5, the rejections of such claims under 35 U.S.C. 102(b) as being anticipated by Eisel, et al. (1993) EMBO J., 12(9): 3365-72, are rendered moot, and thus, are withdrawn.

In light of Applicant's amendments and arguments, the rejections of Claims 1-2 and 4 under 35 U.S.C. 102(b) as being anticipated by Eisel, et al. (1993) EMBO J., 12(9): 3365-72, are withdrawn.

Conclusion

No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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